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(54) Title: NEW USE OF 4, 5, 6, 7-TETRAHYDROIMIDAZO-[4,5-C]PYRIDINE DERIVATIVES

(57) Abstract: The invention relates to the use of compounds of Formula (I), in which R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are as described in the  
specification, for the treatment or prophylaxis of SSAO-mediated complications, such as diabetes.

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## NEW USE

## TECHNICAL FIELD

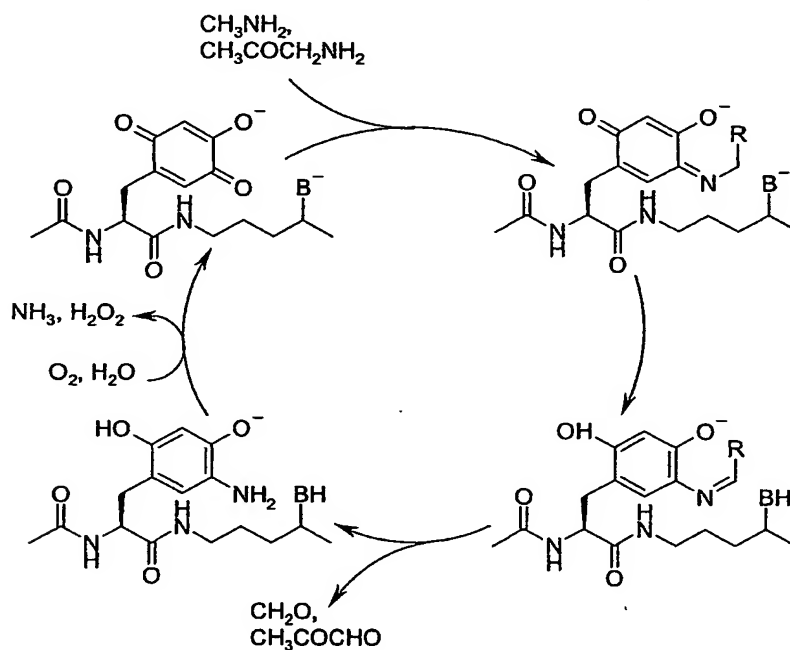
The present invention relates to use of 4-alkyl-5-alkoxycarbonyl-4, 5, 6, 7-tetrahydroimidazo[4,5-c] pyridine derivatives for the manufacture of medicaments for, or treatment or prophylaxis of semicarbazide-sensitive amine oxidase (SSAO)-mediated complications.

## BACKGROUND ART

Semicarbazide-sensitive amine oxidase, SSAO, is a monoamine oxidase that recently has been suggested to be responsible for microvascular complications in diabetic patients. Nephropathy, neuropathy and retinopathy represent the end results of microvascular complications in both insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM). Heart attack, angina, strokes, amputations, blindness and renal failure are clinical events that represent the end point of the clinical study. Endothelial cells dysfunction may precede the diabetic state of complications. The SSAO enzyme is located in the vascular smooth muscles, retina, kidney and the cartilage tissues, and in the circulating blood (Yu, P. H. Deamination of methylamine and angiopathy; toxicity of formaldehyde, oxidative stress and relevance to protein glycooxidation in diabetes. *J. Neural. Transm. Suppl.*, 1998, 52, 201) and has been found to be overactive in diabetic patients (Ekblom, J. Potential therapeutic value of drugs inhibiting semicarbazide-sensitive amine oxidase: vascular cytoprotection in diabetes mellitus. *Pharmacol. Res.*, 1998, 37, 87). SSAO oxidizes a primary amine into the corresponding aldehyde with the help of the non-proteogenic amino acid topaquinone (*Scheme 1*). Oxidation of the aminophenol form of topaquinone into the quinone form, in order to close the catalytic cycle, is catalyzed by Cu(II), present in the active site of the enzyme. Hydrogen peroxide and ammonia are produced. The general catalytic cycle is very similar to the one observed for other monoamine oxidases (*Scheme 1*). The higher activity of SSAO as well as the higher concentration of its natural substrates, methylamine and aminoacetone, in diabetic patients, would lead to a higher production of formaldehyde, methylglyoxal and hydrogen peroxide. These products are known to be highly cytotoxic for the endothelial cell layer and might lead to the observed microvascular complication in diabetic patients (Yu, P. H. Deamination of methylamine and angiopathy; toxicity of formaldehyde, oxidative stress and

relevance to protein glycoxidation in diabetes. *J. Neural. Transm. Suppl.*, 1998, 52, 201). The inhibition of SSAO-mediated reactions is therefore a strategy that could be beneficial for a variety of pathological conditions.

*Scheme 1*: SSAO's catalytic cycle. The active site is represented schematically by the topaquinone residue as well as by a basic amino acid residue B<sup>+</sup> essential for the activity.

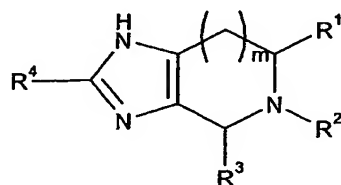


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## SUMMARY OF THE INVENTION

According to the invention a method of treatment or prophylaxis of SSAO-mediated complications in mammals including humans is provided. The method comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of Formula (I):

15



(I)

or a pharmaceutically acceptable salt thereof, wherein

R<sup>1</sup> is

- (a) H, or
- (b) CONH-R<sup>5</sup>;

5 R<sup>2</sup> is

- (a) COOR<sup>5</sup>,
- (b) COR<sup>5</sup>,
- (c) CONH-R<sup>5</sup>,
- (d) CSNH-R<sup>5</sup>, or
- 10 (e) H;

R<sup>3</sup> is

- (a) H,
- (b) C<sub>1-8</sub> alkyl, or
- (c) (CH<sub>2</sub>)<sub>n</sub>Ar;

15 R<sup>4</sup> is

- (a) H,
- (b) Ar, or
- (c) C<sub>1-8</sub> alkyl; and

R<sup>5</sup> is

- 20 (a) H,
- (b) (CH<sub>2</sub>)<sub>n</sub>Ar,
- (c) (CH<sub>2</sub>)<sub>n</sub>OAr,
- (d) C<sub>1-8</sub> alkyl containing 0-2 oxygen atoms and optionally substituted with 0-5  
halogen atoms, or
- 25 (e) a polyether chain having the formula (CH<sub>2</sub>)<sub>x</sub>O(CH<sub>2</sub>)<sub>y</sub>O(CH<sub>2</sub>)<sub>z</sub>CH<sub>3</sub>;

n is an integer 0 to 4;

m is an integer 0 to 2;

x and y are integers 2 to 4;

z is an integer 0 to 3;

30 Ar is phenyl, 1-naphthyl or 2-naphthyl, unsubstituted optionally mono-or poly-substituted with electrodonating groups, halogen, C<sub>1-6</sub> alkyl, CF<sub>3</sub>, hydroxyl, C<sub>1-6</sub> alkoxy, OCF<sub>3</sub>, CN, NO<sub>2</sub>, phenyloxy, benzyloxy, optionally substituted phenyl, alkylsulfonyl, C<sub>1-6</sub> alkenyl, -NH<sub>2</sub>, R<sup>7</sup>NH-, R<sup>7</sup>R<sup>7</sup>N-, C<sub>1-6</sub> alkylcarboxyl, formyl, C<sub>1-6</sub>

alkyl-CO-NH-, aminocarbonyl ( $R^7 R^7-N-CO-$ ),  $SR^7$  wherein  $R^7$  is simultaneously or alternatively H or  $C_{1-6}$  alkyl; cinnamoyl, unsubstituted or optionally substituted benzyl; 1,1-diphenylethyl, a monocyclic or bicyclic heterocyclic ring (furyl, pyrrolyl, triazolyl, diazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyridyl, 5 pyrimidyl, pyrazinyl, thienyl, imidazolyl, pyrazolyl, indolyl, quinoliny, isoquinoliny, benzofuryl, benzothienyl, benzoxadiazolyl which are unsubstituted or optionally mono or di-substituted with halogen,  $C_{1-6}$  alkyl); 2, or 3, or 4-pyridyl or a 5 to 7-membered unsaturated or partially or completely saturated heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur where nitrogen containing 10 heterocycles may contain H or  $C_{1-6}$  alkyl or  $CF_3-CO-$  at the nitrogen atoms where such a substitution is allowed.

The term " $C_{1-8}$  alkyl" denotes a saturated or unsaturated, straight, branched or cyclic alkyl group having from 1 to 8 carbon atoms. Examples of said  $C_{1-8}$  alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, and straight- 15 and branched-chain pentyl, hexyl, septyl and octyl, optionally substituted with 0-5 halogen atoms.

The term "halogen" shall mean fluorine, chlorine, or bromine.

#### DETAILED DESCRIPTION OF THE INVENTION

20 According to the present invention it has been found that 4-alkyl-5-alkoxycarbonyl-4,5,6,7-tetrahydroimidazo[4,5-c] pyridine derivatives of Formula (I) are potent compounds for inhibiting SSAO-mediated reactions.

4-alkyl-5-alkoxycarbonyl-4,5,6,7-tetrahydroimidazo[4,5-c] pyridine derivatives are known from GB 2 158 440 and U.S. 4,223,146. In the GB application the 25 compounds are disclosed to have anti-viral activity. The compounds in the U.S. patent are useful as antiulcer agents and as inhibitors of gastric secretion.

In Formula (I) preferred substituents are as follows:

$R^1$  is H,  $CO-NH_2$ ,  $R^3$  is  $C_{1-3}$  alkyl or benzyl and  $R^2$  is  $COOR^5$  and  $R^5$  is

1) H or a linear, branched or cyclic  $C_{1-8}$  alkyl which can be saturated or not, 30 containing 0-2 oxygen atoms and optionally substituted with 0-5 halogen atoms;

2)  $(CH_2)_nAr$ , where  $n = 0-3$  and Ar is a phenyl group or a phenyl group substituted with electrodonating groups and/or halogen atoms.

Preferred compound of Formula (I) are:

benzyl 4-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate;

benzyl 4-ethyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate  
trifluoroacetate;

5        benzyl 4-propyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate  
trifluoroacetate;

2,2,2-trichloroethyl 4-ethyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-  
carboxylate; and

benzyl (4S,6S)-6-(aminocarbonyl)-4-ethyl-1,4,6,7-tetrahydro-  
10    5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate.

The compounds of the Formula (I) can form acid addition salts with acids such  
as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric,  
hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and  
methanesulfonic.

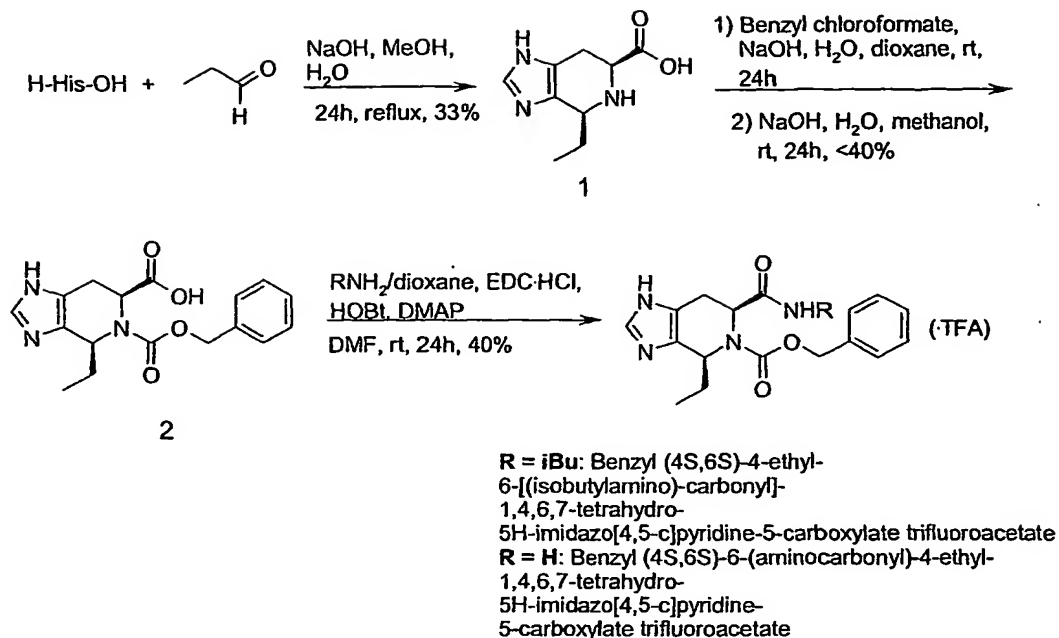
15        Compounds of Formula (I) may also form solvates such as hydrates and the  
invention also extends to these forms. When referred to herein, it is understood that the  
term "compound of Formula (I)" also includes these forms.

Certain compounds of Formula (I) are capable of existing in stereoisomeric  
forms including diastereomers and enantiomers and the invention extends to each of  
20    these stereoisomeric forms and to mixtures thereof including racemates. The different  
stereoisomeric forms may be separated one from the other by the usual methods. Any  
given isomer may be obtained by stereospecific or asymmetric synthesis. The invention  
also extends to any tautomeric forms and mixtures thereof.

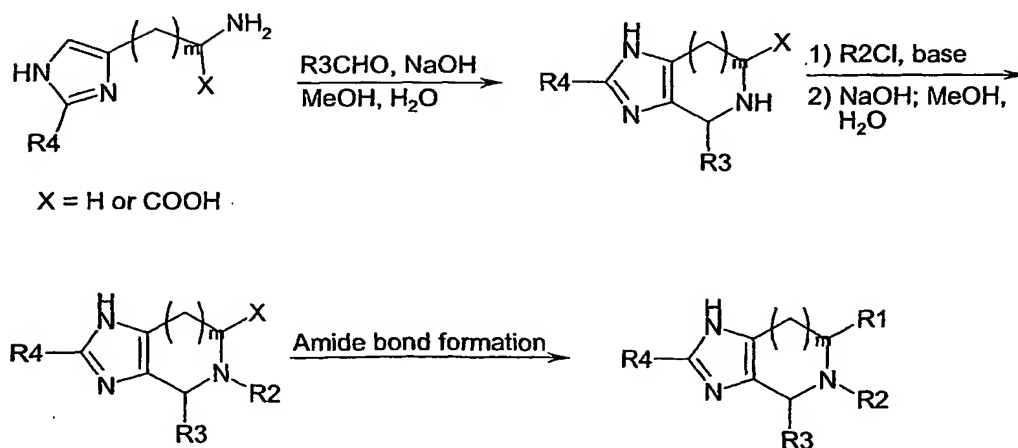
Preferably the compounds of Formula (I) are used for treatment or prophylaxis  
25    of SSAO mediated vascular complications and for insulin dependent diabetes mellitus  
and non-insulin dependent diabetes mellitus.

The compounds used in the invention are prepared according to known methods.  
The compounds can be prepared as follows:

Scheme 2:



Scheme 3:



The starting materials are commercially available or can be prepared following known procedures.

According to the present invention the compounds for treatment of SSAO mediated complications can conveniently be administered in a pharmaceutical composition containing the compound in combination with a suitable excipient. Such pharmaceutical compositions can be prepared by methods and contain excipients which are well known in the art. A generally recognized compendium of such methods and

ingredients is Remington's Pharmaceutical Sciences by E.W. Martin (Mark Publ. Co., 15<sup>th</sup> Ed., 1975). The compounds and compositions can be administered orally, parenterally (for example, by intravenous, intraperitoneal or intramuscular injection), topically, or rectally.

5        Useful dosages of the compounds of Formula (I) can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known in the art; for example, see U.S. Pat. No. 4,938,949.

      The compound can be administered in unit dosage form; for example, containing  
10    about 0.05 mg to about 500 mg, conveniently about 0.1 mg to about 250 mg, most conveniently, about 1 mg to about 150 mg of active ingredient per unit dosage form. The desired dose may be presented in a single dose or as divided doses administered at appropriate intervals. The compositions can be administered orally, sublingually, transdermally, or parenterally at dose levels of about 0.01 to about 150 mg/kg,  
15    preferably about 0.1 to about 50 mg/kg, and more preferably about 0.1 to about 30 mg/kg of mammal body weight.

      The invention will now be illustrated with the following examples, which however, are not intended to limit the scope of the invention.

      The following abbreviations are used:

20    aq: aqueous; br: broad; DIPEA: diisopropylethylamine; DMAP: 4-(*N,N*-dimethylamino)pyridine; ECAO: *Esterichia Coli* amine oxidase; EDC·HCl: *N*-ethyl-*N'*-3(dimethylamino)propylcarbodiimide hydrochloride; EI: electron impact; eq: equivalent; EtOAc: ethyl acetate; HOBt: hydroxybenzotriazol; HTS: high throughput screening;; Mp: melting point; HRMS: high resolution mass spectrum; org: organic;  
25    RP-HPLC: reversed-phase high pressure liquid chromatography; SAR: structure activity relationship; sat: saturated; TLC: thin layer chromatography.

**Experimental:** Solvents were purchased from *Merck* or *Riedel-de Haen*. Chemicals and reagents were purchased from *Aldrich*, *Lancaster* or *Fluka*. The buffer solution (pH 9) was bought from *Merck* (catalogue number 1.09461.1000, boric  
30    acid/KCl/NaOH). TLCs were run using Silicagel60 F<sub>254</sub> plates purchased from *Merck*. TLCs were analyzed by UV or stained with a solution of KMnO<sub>4</sub> in water. Flash chromatography was run using Silicagel 60 (230-400 mesh) from *Merck*. Parallel flash chromatography was run on a Foxy-200 system from *Isco Inc.* with 108-disposable



columns for FC from *Isco Inc.* RP-HPLCs were run on a *Gilson* system, using a 119 UV-detector (214 nm or 254 nm), a 805 manometric module, a 305- and a 306-pumps and a *Vydac* C<sub>18</sub>-column (218TP1022); H<sub>2</sub>O+0.1%TFA/CH<sub>3</sub>CN were used as eluents. Mps were measured with a *Gallenkamp* apparatus and were uncorrected. NMR spectra were recorded on a *Varian Inova 400* instrument. EI-MS spectra were recorded on a JMS SX-102A mass spectrometer (*Jeol*, Tokyo, Jpn) at 70eV or on an Autospec-oaTOF *Micromass Manchester* instrument at 70 eV. HRMS spectra were recorded on a LCT *Micromass* instrument with flow injection-electrospray positive mode; quaternary ammonium salts were used as references. Reactions were followed by MS, using a Platform I *Micromass* instrument, Manchester, with an electrospray positive and negative mode flow injection. Elemental analysis was run on an *Elementar* Vario EL instrument.

*General Procedure I (GPI):* A solution of histidine or histamine, NaOH and aldehyde was prepared in water and MeOH, and was heated under reflux for 24 h. After cooling the solution to room temperature, then to 0°C, aq. conc. HCl was added. See the specific examples for the work-up procedures.

*General procedure II (GP II):* A solution of tetrahydroimidazopyridine and K<sub>2</sub>CO<sub>3</sub> in CHCl<sub>3</sub> and water was cooled to 0°C. The chloroformate, resp. the acyl chloride was added dropwise. The mixture was stirred for 24 h while warming up to room temperature. The phases were separated, the org. phase dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent removed under reduced pressure. The residue was dissolved or suspended in MeOH (3 mL/mmol of starting material) and aq. 1M NaOH (2 mL/mmol of starting material) was added. After 1 h, the mixture was worked-up and purified, see specific examples.

Carboxylic acid Intermediate (scheme 2)

**(4*S*,6*S*)-4-Ethyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-*c*]pyridine-6-carboxylic acid:** According to *GPI* with histidine (15.5 g, 0.100 mol), NaOH (24 g, 0.60 mol), water (100 mL), MeOH (400 mL) and propionaldehyde (20 mL, 0.276 mol). The solution was then acidified to pH 7-8 with aq. conc. HCl (60 mL) and the solvent was removed under reduced pressure. After drying the residue thoroughly under high vacuum, the oil was triturated with hot EtOH and filtered (3x). The filtrate was evaporated under reduced pressure and the residue crystallised from EtOH/water. **(4*S*,6*S*)-4-Ethyl-4,5,6,7-tetrahydro-3H-imidazo[4,5-*c*]pyridine-6-carboxylic acid** was isolated as a white

powder (6.44 g, 33%). <sup>1</sup>H-NMR and NOE-measurement showed a *cis/trans* ratio of 9:1. Mp = 242-4 °C. <sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O; only *cis*-stereoisomer described): δ = 7.75 (s, 1H); 4.43 (m, br., 1H); 4.05 (dd, *J*<sub>1</sub> = 12.1 Hz, *J*<sub>2</sub> = 5.2 Hz, 1 H); 3.81 (dd, *J*<sub>1</sub> = 16.5 Hz, *J*<sub>2</sub> = 5.3 Hz, 1H); 3.00 (ddd, *J*<sub>1</sub> = 16.5 Hz, *J*<sub>2</sub> = 12.1 Hz, *J*<sub>3</sub> = 2.4 Hz, 1H); 2.27 (m, 1H); 1.91 (m, 1H); 1.14 (t, *J* = 7.6 Hz, 3H). <sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): δ = 173.28 (s); 137.27 (d); 129.83 (s); 124.10 (s); 57.98 (d); 56.20 (d); 25.17 (t); 23.79 (t); 9.51 (q). MS (EI): *m/z* = 194 (M<sup>+</sup>-H<sub>2</sub>, 2%); 166 (61%); 148 (9%); 120 (100%); 107 (10%); 93 (10%). HRMS: Calc. for C<sub>9</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>: M<sup>+</sup> = 195.1008; found: M<sup>+</sup> = 195.0000.

#### Intermediate 2 (Scheme 2)

**(4*S*,6*S*)-5-[(Benzyloxy)carbonyl]-4-ethyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine-6-carboxylic acid:** A solution of **(4*S*,6*S*)-4-Ethyl-4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridine-6-carboxylic acid** (500 mg, 2.56 mmol) in an aq. buffer solution at pH9 (5 mL) and dioxane (1 mL) was cooled to 0 °C. Benzyl chloroformate (0.845 mL, 5.64 mmol) was added dropwise over 1 min. The pH was maintained between 7 and 9 by adding from time to time aq. 1M NaOH (total amount: about 5 mL). The mixture was stirred overnight while the temperature rose slowly to room temperature. The final pH was equal to 6.5 and an oily precipitate was lying in the bottom of the flask. This oily precipitate was decanted, dissolved in CHCl<sub>3</sub> and the solution dried over MgSO<sub>4</sub>. After filtration, the filtrate was evaporated under reduced pressure. The residue was diluted in MeOH (20 mL) and aq. 1M NaOH was added (10 mL). This solution was stirred at room temperature overnight and the pH was brought to 7 with aq. 1M HCl. The solvent was removed under reduced pressure and the residue dried under high vacuum. The dried residue was purified by RP-HPLC (C<sub>18</sub>-column, 95% H<sub>2</sub>O → 75% H<sub>2</sub>O over 10 min → 0% H<sub>2</sub>O over 10min). The acid was obtained as a foam (224 mg, 40%). <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD): δ = 8.15 (s, br., 1H); 7.40-7.23 (m, 5H); 5.46 (s, br., 1H); 5.21 (s, br., 3H); 2.83 (dd, *J*<sub>1</sub> = 15.6 Hz, *J*<sub>2</sub> = 6.1 Hz, 1H); 1.79 (s, br., 2H); 1.05 (s, br., 3H). MS (pos. ionization): *m/z* = 330 (MH<sup>+</sup>).

#### Example 1:

##### **4-Methyl-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*c*]pyridine dihydrochloride:**

According to *GPI* with histamine dihydrochloride (12.1 g, 0.109 mol), NaOH (10.9 g, 0.272 mol), water (100 mL), MeOH (450 mL) and acetaldehyde (15.5 mL, 0.276 mol). The solution was acidified to pH<1 with aq. conc. HCl and the solvent was removed under reduced pressure. The residue was thoroughly dried under high vacuum. The

resulting oil was triturated with MeOH (1x 150 mL, 2x 50 mL) and filtered. The filtrate was evaporated under reduced pressure and the residue dried under high vacuum. This residue was then suspended in <sup>1</sup>PrOH and this suspension refluxed for 1h. After allowing it to cool to room temperature, the mixture was filtered and the precipitate  
5 dried under high vacuum. The product was obtained as a brown powder that was not purified further (21.2 g, 90%). <sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O):  $\delta$  = 8.70 (s, br., 1H); 3.76 (m, br., 1H); 3.53 (m, br., 1H); 3.09 (s, br., 2H); 1.69 (s, br., 3H).

Example 2:

**4-Ethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride:**

10 According to *GPI* with histamine dihydrochloride (20.0 g, 0.109 mol), NaOH (19.6 g, 0.49 mol), water (100 mL), MeOH (450 mL) and propionaldehyde (20.0 mL, 0.276 mol). The reaction mixture was acidified to pH<1 with aq. conc. HCl (200 mL) and the solvent was removed under reduced pressure. The residue was dried thoroughly under high vacuum and the resulting oil triturated with MeOH (1x150 mL and 2x50 mL). The  
15 filtrate was evaporated under reduced pressure and the residue dried under high vacuum. The resulting oil was triturated with EtOH (1x50 mL and 2x15 mL) and filtered. The precipitate was dried under high vacuum. **4-Ethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride** was obtained as a colorless powder (5.38 g, 22%). <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$  = 8.95 (s, 1H); 4.69-4.61 (m, 1H); 3.80-3.70 (m, 1H); 3.55-3.46 (m, 1H); 3.20-3.02 (m, 2H); 2.31-2.15 (m, 1H); 2.05-1.92 (m, 1H); 1.15  
20 (t, *J* = 7.8 Hz, 3H). <sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O):  $\delta$  = 134.70 (d); 124.98 (s); 123.72 (s); 53.26 (d); 40.59 (t); 24.41 (t); 18.11 (t); 8.88 (q). MS (EI): *m/z* = 151 (*M*<sup>+</sup>, 1%); 150 (2%); 122 (100%); 107 (5%); 95 (13%); 80 (3%). HRMS: calc. for C<sub>8</sub>H<sub>13</sub>N<sub>3</sub>: *M*<sup>+</sup> = 151.1158; found: 151.1109.

25 Example 3:

**4-Propyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride:**

According to *GPI* with histamine dihydrochloride (20.0 g, 0.109 mol), NaOH (19.6 g, 0.49 mol), water (100 mL), MeOH (450 mL) and butyraldehyde (24.9 mL, 0.278 mol). The reaction mixture was acidified to pH<1 with aq. conc. HCl (200 mL) and the  
30 solvent was removed under reduced pressure. The residue was dried thoroughly under high vacuum and the resulting oil triturated with MeOH (1x150 mL and 2x50 mL). The filtrate was evaporated under reduced pressure and the residue dried under high vacuum. The resulting oil was triturated with EtOH (1x50 mL and 2x15 mL) and

filtered. The precipitate was dried under high vacuum. **4-Propyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride** was obtained as a colorless powder (20.9g, 80%). <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD): δ = 8.99 (s, 1H); 4.75 (dd, *J*<sub>1</sub> = 9.0 Hz, *J*<sub>2</sub> = 4.4 Hz, 1H); 3.82-3.73 (m, 1H); 3.59-3.50 (m, 1H); 3.24-3.05 (m, 2H); 2.21-2.10 (m, 1H); 2.04-1.90 (m, 1H); 1.70-1.52 (m, 2H); 1.07 (t, *J* = 7.8 Hz, 3H). <sup>13</sup>C-NMR (100 MHz, CD<sub>3</sub>OD): δ = 136.13 (d); 126.43 (s); 125.61 (s); 53.05 (d); 41.79 (t); 34.41 (t); 19.45 (t); 19.30 (t); 14.01 (q). MS (EI): *m/z* = 165 (*M*<sup>+</sup>, 1%); 164 (2%); 135 (2%); 122 (100%); 95 (12%); 80 (2%); 68 (5%).

Example 4:

**4-Phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride:**  
According to *GPI* with histamine (10.0 g, 90 mmol), NaOH (9.0 g, 225 mol), water (90 mL), MeOH (365 mL) and benzaldehyde (23.1 mL, 0.23 mol). The reaction mixture was acidified to pH<1 with aq. conc. HCl (165 mL) and the solvent was removed under reduced pressure. The residue was dried thoroughly under high vacuum and the resulting oil triturated with hot <sup>1</sup>PrOH (150 mL). The mixture was filtered and the precipitate washed with cold <sup>1</sup>PrOH (2x30 mL). The filtrate was heated to reflux and hexane (210 mL) added slowly, whereas a precipitate formed. The mixture was cooled to room temperature, then to -18 °C. The precipitate was filtered and dried. **4-Phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride** was obtained as a yellow powder that contained 0.7 eq of <sup>1</sup>PrOH (14.1 g, 12.2 g of product, 50%). <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD): δ = 8.96 (s, 1H); 7.6-7.3 (m, 5H); 5.99 (s, 1H); 3.75-3.60 (m, 2H); 3.38-3.30 (m, 1H); 3.20 (dt, *J*<sub>1</sub> = 16.6 Hz, *J*<sub>2</sub> = 5.5 Hz, 1H). <sup>13</sup>C-NMR (100 MHz, D<sub>2</sub>O): δ = 135.25 (s); 131.33 (d); 129.84 (d); 129.45 (d); 126.47 (s); 122.81 (s); 55.45 (d); 40.18 (t); 18.17 (t). MS (EI): *m/z* = 199 (*M*<sup>+</sup>, 5%); 170 (100%); 122 (89%); 91 (3%). HRMS; Calc. for C<sub>12</sub>H<sub>13</sub>N<sub>3</sub>: *M*<sup>+</sup> = 199.1107; found: 199.1109.

Example 5:

**4-Benzyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride (3):**  
According to *GPI* with histamine dihydrochloride (20.0 g, 0.109 mol), NaOH (19.6 g, 0.49 mol), water (100 mL), MeOH (450 mL) and phenacetaldehyde (36 mL, 0.276 mol). The reaction mixture was acidified to pH<1 with aq. conc. HCl (50 mL) and the solvent was removed under reduced pressure. The residue was dried thoroughly under high vacuum and the resulting oil triturated with MeOH (1x150 mL and 2x50 mL). The filtrate was evaporated under reduced pressure and the residue dried under high

vacuum. The resulting oil was triturated with <sup>1</sup>PrOH and filtered. The precipitate was dried under high vacuum. **4-Benzyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride** was obtained as a colorless powder that still contained 1 eq. <sup>1</sup>PrOH (31.9 g, 25 g of product, 96%). <sup>1</sup>H-NMR (400 MHz, D<sub>2</sub>O): δ = 8.76 (s, 1H); 7.52-7.43 (m, 3H); 7.40-7.35 (m, 2H); 5.07 (dd, *J*<sub>1</sub> = 9.1 Hz, *J*<sub>2</sub> = 5.7 Hz, 1H); 3.76 (dt, *J*<sub>1</sub> = 13.1 Hz, *J*<sub>2</sub> = 5.2 Hz, 1H); 3.63 (dd, *J*<sub>1</sub> = 14.4 Hz, *J*<sub>2</sub> = 5.6 Hz, 1H); 3.53 (ddd, *J*<sub>1</sub> = 13.9 Hz, *J*<sub>2</sub> = 7.6 Hz, *J*<sub>3</sub> = 6.1 Hz, 1H); 3.24 (dd, *J*<sub>1</sub> = 14.2 Hz, *J*<sub>2</sub> = 9.3 Hz, 1H); 3.16 (dd, *J*<sub>1</sub> = 12.9 Hz, *J*<sub>2</sub> = 7.8 Hz, 1H).

Example 6:

**Methyl 4-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate:** According to *GPII*, starting from **4-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride** (500 mg, 2.38 mmol), K<sub>2</sub>CO<sub>3</sub> (690 mg, 5.00 mmol), CHCl<sub>3</sub> (6 mL), H<sub>2</sub>O (3 mL) and methyl chloroformate (0.39 mL, 5.0 mmol). The reaction was carried out in a parallel fashion in a test-tube closed with a screwed tap and stirred in a *Stem*-stirrer. The basic treatment was carried out in MeOH (6 mL) and aq. 1M NaOH (4 mL). After 1 h the mixture was acidified with aq. 1M HCl (3 mL). The reaction mixture was evaporated in a speed-vac overnight. The residue was triturated with CHCl<sub>3</sub> and filtered several times. The combined org. phases were evaporated in a speed-vac. The residue was purified by parallel FC with a gradient pump (MeOH/CHCl<sub>3</sub> 0:100 → 0:100 for 5 min, then → 1:3 over 25 min). **Methyl 4-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate** was obtained as foam (270 mg, 58%). *R*<sub>f</sub> = 0.30 (MeOH/CHCl<sub>3</sub> 1:9). <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD): δ = 7.52 (s, 1H); 4.99 (s, br., 1H); 4.30 (s, br., 1H); 3.71 (s, 3H); 3.15 (td, br., *J*<sub>1</sub> = 11.7 Hz, *J*<sub>2</sub> = 3.7 Hz, 1H); 2.67 (m, 1H); 2.54 (dd, *J*<sub>1</sub> = 15.6 Hz, *J*<sub>2</sub> = 4.2 Hz, 1H); 1.88 (d, *J* = 6.8 Hz, 3H). <sup>13</sup>C-NMR (100 MHz, CD<sub>3</sub>OD): δ = 157.47 (s); 135.38 (d); 134.32 (s); 126.41 (s); 53.37 (q); 49.43 (d); 38.71 (t); 23.50 (t); 19.28 (q). MS (EI): *m/z* = 195 (*M*<sup>+</sup>, 11%); 180 (100%); 136 (10%); 120 (16%); 107 (22%). HRMS: Calc. for C<sub>9</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>: *M*<sup>+</sup> = 195.1008; found: 195.1010.

Example 7:

**Benzyl 4-ethyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate:** According to *GPII*, starting from **4-ethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride** (1.00 g, 4.48 mmol), K<sub>2</sub>CO<sub>3</sub> (1.24 g, 9.0 mmol), CHCl<sub>3</sub> (10 mL), H<sub>2</sub>O (8 mL) and benzyl chloroformate (1.36 mL, 9.0 mmol). After

basic treatment for 1 h the mixture was acidified to pH 8-8.5 with aq. 1M HCl. The reaction mixture was extracted with  $\text{CHCl}_3$  (4x) and the combined org. phases were dried over  $\text{Na}_2\text{SO}_4$ . The solvent was removed under reduced pressure. Twice successively, the residue was treated with aq. 1M HCl and the solvent removed under reduced pressure. The residue was then suspended in aq. 1M HCl (15 mL) and washed with  $\text{Et}_2\text{O}$  (2x). The aq. phase was evaporated under reduced pressure and the residue purified by RP-HPLC (95%  $\text{H}_2\text{O} \rightarrow 0\% \text{H}_2\text{O}$  over 20 min). **Benzyl 4-ethyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate** was obtained as foam (590 mg, 33%).  $^1\text{H}$ -NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  = 8.75 (s, 1H); 7.42-7.27 (m, 5H); 5.19 (s, br., 3H); 4.46 (m, br., 1H); 3.25 (m, br., 1H); 2.78 (m, br., 1H); 2.69 (dd,  $J_1$  = 15.4 Hz,  $J_2$  = 3.4 Hz, 1H); 1.00 (s, br., 3H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  = 134.09 (d); 129.46 (d); 129.19 (d); 68.90 (t); 52.60 (d); 38.25 (t); 28.04 (t); 10.86 (q). MS (EI):  $m/z$  = 285 ( $\text{M}^+$ , 0.4%); 256 (45%); 194 (34%); 150 (5%); 120 (9%); 107 (5%); 91 (100%). HRMS: Calc. for  $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_2$ :  $\text{M}^+$  = 285.1477; found: 285.1471. Elemental analysis: Calc. for  $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_2 \cdot \text{C}_2\text{HF}_3\text{O}_2 \cdot \text{H}_2\text{O}$ : C 51.8%, H 5.3%, N 10.6%; found: C 52.0%, H 4.9%, N 9.8%.

Example 8:

**Benzyl 4-phenyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate:** According to *GPII*, starting from **4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride** (800 mg, 2.54 mmol),  $\text{K}_2\text{CO}_3$  (737 mg, 5.33 mmol),  $\text{CHCl}_3$  (6 mL),  $\text{H}_2\text{O}$  (5 mL) and benzyl chloroformate (0.80 mL, 5.33 mmol). After basic treatment for 1 h the mixture was acidified to pH 8 with aq. 1M HCl. The reaction mixture was extracted with  $\text{CHCl}_3$  (4x) and the combined org. phases were dried over  $\text{Na}_2\text{SO}_4$ . The solvent was removed under reduced pressure and the residue purified by RP-HPLC (95%  $\text{H}_2\text{O} \rightarrow 0\% \text{H}_2\text{O}$  over 20 min). **Benzyl 4-phenyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate** was obtained as foam (291 mg, 25%) that contained 0.65 eq.  $\text{H}_2\text{O}$  according to the elemental analysis.  $t_R$  = 11.26 min.  $^1\text{H}$ -NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  = 8.83 (s, 1H); 7.48-7.27 (m, 10H); 6.48 (s, br., 1H); 5.26 (d, br.,  $J$  = 10.8 Hz, 1H); 5.18 (d,  $J$  = 12.0 Hz, 1H); 4.38 (d, br.,  $J$  = 12.2 Hz, 1H); 3.20 (ddd,  $J_1$  = 15.9 Hz,  $J_2$  = 11.2 Hz,  $J_3$  = 4.6 Hz, 1H); 2.96-2.78 (m, 2H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  = 139.04 (s); 137.49 (s); 134.91 (d); 129.89-128.98 (several peaks, d and s); 127.85 (s); 69.11 (t); 54.16 (d); 38.12 (t); 22.24 (t). MS (EI):  $m/z$  = 333 ( $\text{M}^+$ , 9%); 242 (89%); 212 (4%); 198

(61%); 169 (27%); 91 (100%). Elemental analysis: Calc. for  $C_{20}H_{19}N_3O_2 \cdot C_2HF_3O_2 \cdot 2/3H_2O$ : C 57.5%, H 4.7%, N 9.1%; found: C 57.5%, H 4.4%, N 9.1%.

Example 9:

- 5 **Benzyl 4-benzyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate:**  
According to *GPII*, starting from 4-benzyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride (500 mg, 1.74 mmol),  $K_2CO_3$  (507 mg, 3.67 mmol),  $CHCl_3$  (6 mL),  $H_2O$  (3 mL) and benzyl chloroformate (0.55 mL, 3.67 mmol). The reaction was carried out in a parallel fashion in a test-tube closed with a screwed tap and stirred in a *Stem*-stirrer. The basic treatment was carried out in MeOH (6 mL) and aq. 1M NaOH (4 mL). After 1 h the mixture was acidified with aq. 1M HCl (3 mL). The reaction mixture was evaporated in a speed-vac overnight. The residue was triturated with  $CHCl_3$  and filtered several times. The combined org. phases were evaporated in a speed-vac. The residue was purified by parallel FC with a gradient pump
- 10 (MeOH/ $CHCl_3$  0:100  $\rightarrow$  0:100 for 5 min, then  $\rightarrow$  1:3 over 25 min). **Benzyl 4-benzyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate** was obtained as foam (225 mg, 42%).  $R_f = 0.31$  (MeOH/ $CHCl_3$  1:9).  $^1H$ -NMR (400MHz,  $CD_3OD$ ):  $\delta = 7.57$  (s, 1H); 7.23, 7.15 and 7.03 (m, 10H, rot.); 5.33, 5.25, 5.08 and 4.95 (m, 2H, rot.); 4.84 and 4.60 (d,  $J = 12.2$  Hz, 1H, rot.); 4.81 and 4.17 (dd,  $J_1 = 13.2$  Hz and 13.7 Hz,  $J_2 = 5.4$  Hz and 4.6 Hz, 1H, rot.); 3.24-2.90 (m, 3H, rot.); 2.83-2.33 (m, 2H, rot.).  $^{13}C$ -NMR (100 MHz,  $CD_3OD$ ):  $\delta = 157.24$  and 156.95 (s, rot.); 139.24 and 138.79 (s, rot.); 137.46 (s); 135.51 and 135.46 (d, rot.); 130.44 (d); 129.39, 129.24, 129.13, 129.01, 128.93, 128.83 and 128.72 (3xd, rot.); 127.36 (d); 68.31 and 68.17 (t, rot.); 55.24 and 54.53 (d, rot.); 40.96 and 40.20 (t, rot.); 39.73 and 38.97 (t, rot.); 23.39 and 22.88 (t, rot.). MS (EI):  $m/z = 256$  ( $M^+ - C_7H_7$ , 26%); 212 (22%); 91 (100%). HRMS: Calc. for  $C_{21}H_{21}N_3O_2$ :  $M^+ = 347.1634$ ; found: 347.1603.
- 25

Example 10:

- Benzyl 4-propyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate:** According to *GPII*, starting from 4-propyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride (600 mg, 2.52 mmol),  $K_2CO_3$  (720 mg, 5.2 mmol),  $CHCl_3$  (6 mL),  $H_2O$  (5 mL) and benzyl chloroformate (0.78 mL, 5.2 mmol). After basic treatment for 1h the mixture was acidified to pH 8.5 with aq. 1M HCl. The reaction mixture was extracted with  $CHCl_3$  (3x) and the combined org. phases
- 30

were dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure and the residue purified by RP-HPLC (85% H<sub>2</sub>O → 0% H<sub>2</sub>O over 20 min). **Benzyl 4-propyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate** was obtained as foam that was crystallised from Et<sub>2</sub>O (276 mg, 27%). Mp = 166-7 °C. t<sub>R</sub> = 8.46 min. <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD): δ = 8.74 (s); 7.42-7.27 (m, 5H); 5.31 (m, br., 1H); 5.18 (s, br., 2H); 4.44 (m, br., 1H); 3.25 (m, br., 1H); 2.78 (m, br., 1H); 2.68 (dd, J<sub>1</sub> = 15.6 Hz, J<sub>2</sub> = 3.4 Hz, 1H); 1.76 (m, 2H); 1.44 (m, br., 2H); 0.98 (m, br., 3H). <sup>13</sup>C-NMR (100 MHz, CD<sub>3</sub>OD): δ = 156.92 (s); 134.08 (d); 130-128 (several peaks, s and d); 68.93 (t); 51.13 (d); 38.15 (t); 36.74 (t); 22.16 (t); 20.27 (t); 14.07 (q). MS (EI): m/z = 300 (M+H<sup>+</sup>, 20%); 256 (51%); 212 (60%); 208 (28%); 192 (3%); 164 (16%); 120 (12%); 91 (100%). Elemental analysis: Calc. for C<sub>17</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>·C<sub>2</sub>HF<sub>3</sub>O<sub>2</sub>: C 55.2%, H 5.4%, N 10.2%; found C 55.1%, H 5.1%, N 10.0%.

Example 11:

**Methyl 4-ethyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate:** According to *GP11*, starting from 4-ethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride (600 mg, 2.68 mmol), K<sub>2</sub>CO<sub>3</sub> (778 mg, 5.63 mmol), CHCl<sub>3</sub> (6 mL), H<sub>2</sub>O (4 mL) and methyl chloroformate (0.436 mL, 5.63 mmol). After basic treatment for 1 h the mixture was acidified to pH 8 with aq. 1M HCl. The reaction mixture was extracted with CHCl<sub>3</sub> (4x) and the combined org. phases were dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure and the residue purified by RP-HPLC (95% H<sub>2</sub>O over 5 min then → 40% H<sub>2</sub>O over 10 min). **Methyl 4-ethyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate** was obtained as foam (71 mg, 8%). <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD): δ = 8.78 (s, 1H); 4.19 (s, br., 1H); 4.43 (s, br., 1H); 3.75 (s, 3H); 3.22 (m, br., 1H); 2.79 (m, 1H); 2.69 (m, 1H); 1.86 (m, 2H); 1.03 (t, J = 7.6 Hz, 3H). <sup>13</sup>C-NMR (100 MHz, d<sub>6</sub>-DMSO, at 70 °C): δ = 157.77 (s); 134.06 (d); 129.55 (s); 127.63 (s); 53.74 (q); 52.52 (d); 38.09 (t); 27.92 (t); 22.00 (t); 10.81 (q). MS (EI): m/z = 209 (M<sup>+</sup>, 4%); 180 (100%); 150 (4%); 120 (54%); 107 (11%); 94 (15%); 93 (20%); 59 (76%). HRMS: Calc. for C<sub>10</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>: M<sup>+</sup> = 209.1164; found: 209.1171.

Example 12:

**Methyl 4-propyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate:** According to *GP11*, starting from 4-propyl-4,5,6,7-



tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride (600 mg, 2.52 mmol),  $K_2CO_3$  (720 mg, 5.2 mmol),  $CHCl_3$  (6 mL),  $H_2O$  (4 mL) and methyl chloroformate (0.40 mL, 5.2 mmol). After basic treatment for 1 h the mixture was acidified to pH 8-9 with aq. 1M HCl. The reaction mixture was extracted with  $CHCl_3$  (4x) and the combined org. phases were dried over  $Na_2SO_4$ . The solvent was removed under reduced pressure and the residue purified by RP-HPLC (95%  $H_2O \rightarrow 40\% H_2O$  over 15 min). Methyl 4-propyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate was obtained as foam (134 mg, 16%).  $^1H$ -NMR (400 MHz,  $CD_3OD$ ):  $\delta$  = 8.78 (s); 5.29 (s, br., 1H); 4.39 (s, br., 1H); 3.73 (s, 3H); 3.25 (s, br., 1H); 2.80 (m, 1H); 2.70 (dd,  $J_1 = 15.9$  Hz,  $J_2 = 3.9$  Hz, 1H); 1.79 (m, 1H); 1.46 (m, 1H); 1.00 (t,  $J = 7.3$  Hz, 3H).  $^{13}C$ -NMR (100 MHz,  $d_6$ -DMSO, at 70 °C):  $\delta$  = 155.23 (s); 132.46 (d); 127.74 (s); 125.32 (s); 52.35 (q); 49.05 (d); 36.45 (t); 34.90 (t); 20.49 (t); 18.23 (t); 13.12 (q). MS (EI):  $m/z$  = 223 ( $M^+$ , 2%); 194 (0.5%); 192 (1%); 180 (100%); 164 (1%); 148 (1%); 121 (6%); 120 (13%); 107 (4%). HRMS: Calc. for  $C_{11}H_{17}N_3O_2$ :  $M^+$  = 223.1321; found: 223.1323.

**Example 13:**

Methyl 4-phenyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate: According to *GPII*, starting from 4-phenyl-1,4,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride (800 mg, 2.54 mmol),  $K_2CO_3$  (737 mg, 5.33 mmol),  $CHCl_3$  (8 mL),  $H_2O$  (5 mL) and methyl chloroformate (0.412 mL, 5.33 mmol). After basic treatment for 1 h the mixture was acidified to pH 8 with aq. 1M HCl. The reaction mixture was extracted with  $CHCl_3$  (4x) and the combined org. phases were dried over  $Na_2SO_4$ . The solvent was removed under reduced pressure and the residue purified by RP-HPLC (95%  $H_2O \rightarrow 40\% H_2O$  over 15 min). Methyl 4-phenyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate was obtained as foam (506 mg, 54%) that contained 1 eq water according to the elemental analysis.  $^1H$ -NMR (400 MHz,  $CD_3OD$ ):  $\delta$  = 8.84 (s); 7.47-7.24 (m, 5H); 6.46 (s, br., 1H); 4.34 (d, br.,  $J = 11.2$  Hz, 1H); 3.79 (s, 3H); 3.18 (ddd,  $J_1 = 15.9$  Hz,  $J_2 = 11.2$  Hz,  $J_3 = 4.6$  Hz, 1H); 2.96-2.86 (m, 1H); 2.82 (dd,  $J_1 = 15.6$  Hz,  $J_2 = 3.7$  Hz, 1H).  $^{13}C$ -NMR (100 MHz,  $d_6$ -DMSO, at 70 °C):  $\delta$  = 154.83 (s); 138.18 (s); 133.75 (d); 128.33 (d); 127.99 (d); 127.26 (d); 127.15 (s); 125.44 (s); 52.56 (q); 52.26 (d); 36.58 (t); 20.64 (t). MS (EI):  $m/z$  = 257 ( $M^+$ , 100%); 242 (27%); 226 (7%); 198 (22%); 180 (67%); 121 (6%); 120 (11%). HRMS: Calc. for  $C_{14}H_{15}N_3O_2$ :  $M^+$  =

257.1164; found: 257.1164. Elemental analysis: Calc. for  $C_{14}H_{15}N_3O_2 \cdot C_2HF_3O_2 \cdot H_2O$ : C 49.4%, H 4.7%, N 10.8%; found: C 49.8%, H 4.8%, N 10.4%.

Example 14:

**4-Ethyl-5-(phenoxyacetyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine trifluoroacetate:** According to *GPII*, starting from **4-ethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride** (600 mg, 2.68 mmol),  $K_2CO_3$  (778 mg, 5.63 mmol),  $CHCl_3$  (6 mL),  $H_2O$  (4 mL) and phenoxyacetyl chloride (0.78 mL, 5.6 mmol). After basic treatment for 1 h the mixture was acidified to pH 9 with aq. 1M HCl. The reaction mixture was extracted with  $CHCl_3$  (3x) and the combined org. phases were dried over  $Na_2SO_4$ . The solvent was removed under reduced pressure and the residue purified by RP-HPLC (85%  $H_2O \rightarrow 0\%$   $H_2O$  over 20 min). **4-Ethyl-5-(phenoxyacetyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine trifluoroacetate** was obtained as foam (490 mg, 46%) that contained 1.5 eq.  $H_2O$  according to the elemental analysis.  $t_R = 5.95$  min.  $^1H$ -NMR (400 MHz,  $CD_3OD$ ):  $\delta = 8.72$  (s, 1H); 7.25 (t,  $J = 7.3$  Hz, 2H); 7.08-6.82 (m, 3H); 5.61 (dd,  $J_1 = 9.3$  Hz,  $J_2 = 4.6$  Hz, 0.9H, 1<sup>st</sup> rot.); 4.90-4.70 (m, 2 and 0.2H, 2<sup>nd</sup> rot.); 4.25 (dd,  $J_1 = 14.4$  Hz,  $J_2 = 5.2$  Hz, 0.9H, 1<sup>st</sup> rot.); 3.52 (ddd,  $J_1 = 14.9$  Hz,  $J_2 = 12.0$  Hz,  $J_3 = 4.4$  Hz, 0.9H, 1<sup>st</sup> rot.); 3.17 (m, 0.1H, 2<sup>nd</sup> rot.); 2.93 (m, 1H); 2.76 (m, 1H); 1.10 and 0.97 (t,  $J = 7.3$  Hz, 3H, 2 rot.).  $^{13}C$ -NMR (100 MHz,  $CD_3OD$ ):  $\delta = 170.08$  (s); 159.18 (s); 134.29 (d); 130.48 (d); 129.34 (s); 127.20 (s); 122.60 (d); 115.62 (d); 68.03 (t); 50.38 (d); 39.47 (t); 27.75 (t); 22.86 (t); 10.80 (q). MS (EI):  $m/z = 285$  ( $M^+$ , 15%); 256 (60%); 192 (43%); 178 (4%); 150 (13%); 135 (20%); 107 (45%); 77 (100%). HRMS: Calc. for  $C_{16}H_{19}N_3O_2$ :  $M^+ = 285.1477$ ; found: 285.1472. Elemental analysis: Calc. for  $C_{16}H_{19}N_3O_2 \cdot C_2HF_3O_2 \cdot 3/2H_2O$ : C 50.7%, H 5.4%, N 9.8%; found: C 50.6%, H 5.6%, N 9.4%.

Example 15:

**4-Propyl-5-(phenoxyacetyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine trifluoroacetate:** According to *GPII*, starting from **4-propyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride** (600 mg, 2.52 mmol),  $K_2CO_3$  (720 mg, 5.2 mmol),  $CHCl_3$  (6 mL),  $H_2O$  (4 mL) and phenoxyacetyl chloride (0.72 mL, 5.2 mmol). After basic treatment for 1 h the mixture was acidified to pH 8-9 with aq. 1M HCl. The reaction mixture was extracted with  $CHCl_3$  (4x) and the combined org. phases were dried over  $Na_2SO_4$ . The solvent was removed under reduced pressure and the residue purified by RP-HPLC (80%  $H_2O \rightarrow 0\%$   $H_2O$  over 20 min). **4-Propyl-5-**

(phenoxyacetyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine trifluoroacetate was obtained as foam (307 mg, 30%) that contained 1.5 eq. H<sub>2</sub>O according to elemental analysis.  $t_R$  = 6.36 min. <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$  = 8.74 (s, 1H); 7.30-7.10 (m, 2H); 6.99-6.85 (m, 3H); 5.70 (t,  $J$  = 7.1 Hz, 0.9H, 1<sup>st</sup> rot.); 4.97-4.71 (m, 2H and 0.2H, 2<sup>nd</sup> rot.); 4.27 (dd,  $J_1$  = 14.6 Hz,  $J_2$  = 5.4 Hz, 0.9H, 1<sup>st</sup> rot.); 3.54 (ddd,  $J_1$  = 15.3 Hz,  $J_2$  = 11.7 Hz,  $J_3$  = 4.2 Hz, 0.9H, 1<sup>st</sup> rot.); 3.19 (m, 0.1H, 2<sup>nd</sup> rot.); 2.94 (ddd,  $J_1$  = 16.9 Hz,  $J_2$  = 11.7 Hz,  $J_3$  = 5.4 Hz, 0.9H, 1<sup>st</sup> rot.); 2.78 (dd,  $J_1$  = 16.1 Hz,  $J_2$  = 3.7 Hz, 0.9H, 1<sup>st</sup> rot.); 2.70 (m, 0.2H, 2<sup>nd</sup> rot.); 1.88 (m, 0.1H, 2<sup>nd</sup> rot.); 1.80 (m, 0.9H, 1<sup>st</sup> rot.); 1.52 (m, 0.1H, 2<sup>nd</sup> rot.); 1.39 (m, 0.9H, 1<sup>st</sup> rot.); 1.00 and 0.95 (t,  $J$  = 7.5 Hz, 3H). <sup>13</sup>C-NMR (100MHz, CD<sub>3</sub>OD);  $\delta$  = 170.04 (s); 134.29 (d); 130.49 (d); 129.57 (s); 127.16 (s); 122.63 (d); 115.65 (d); 68.08 (t); 48.86 (d); 39.39 (t); 36.71 (t); 22.89 (t); 20.19 (t); 14.18 (q). MS (EI):  $m/z$  = 299 ( $M^+$ , 21%); 256 (100%); 206 (64%); 192 (4%); 135 (23%); 120 (40%); 107 (39%); 93 (15%). HRMS: Calc. for C<sub>17</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>:  $M^+$  = 299.1634; found: 299.1630. Elemental analysis: Calc. for C<sub>17</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>·C<sub>2</sub>HF<sub>3</sub>O<sub>2</sub>·3/2H<sub>2</sub>O: C 51.8%, H 5.7%, N 9.5%; found: C 51.9%, H 5.6%, N 9.2%.

#### Example 16:

**4-Phenyl-5-(phenoxyacetyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine trifluoroacetate:** According to *GPII*, starting from 4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride (800 mg, 2.54 mmol), K<sub>2</sub>CO<sub>3</sub> (737 mg, 5.33 mmol), CHCl<sub>3</sub> (8 mL), H<sub>2</sub>O (6 mL) and phenoxyacetyl chloride (0.74 mL, 5.33 mmol). After basic treatment for 1 h the mixture was acidified to pH 8-9 with aq. 1M HCl. The reaction mixture was extracted with CHCl<sub>3</sub> (4x) and the combined org. phases were dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure and the residue purified by RP-HPLC (85% H<sub>2</sub>O → 0% H<sub>2</sub>O over 20 min). **4-Phenyl-5-(phenoxyacetyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine trifluoroacetate** was obtained as foam (400 mg, 35%).  $t_R$  = 6.93 min. <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$  = 8.85 (s, 1H); 7.46-7.23 (m, 7H); 7.00-6.86 (m, 3H); 4.96-4.76 (m, 3H); 4.20 (dd,  $J_1$  = 14.4 Hz,  $J_2$  = 4.9 Hz, 1H); 3.45 (m, 1H); 3.06 (m, 1H); 2.91 (d,  $J$  = 15.6 Hz, 1H). <sup>13</sup>C-NMR (100 MHz, d<sub>6</sub>-DMSO):  $\delta$  = 166.72 (s); 157.72 (s); 138.00 (s); 134.10 (d); 129.27 (d); 128.62 (d); 128.32 (d); 127.77 (d); 127.42 (s); 124.84 (s); 120.89 (d); 114.52 (d); 65.93 (t); 49.70 (d); 37.73 (t); 21.59 (t). MS (EI):  $m/z$  = 333 ( $M^+$ , 77%); 256 (4%); 240 (100%); 226 (13%); 198 (56%); 169 (48%); 135 (3%); 122 (8%); 120 (12%); 94 (19%); 77 (73%). HRMS: Calc. for C<sub>20</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>:  $M^+$  = 333.1477; found: 333.1475.

Example 17:

Cyclopentyl 4-ethyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate: According to *GP/II*, starting from 4-ethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride (400 mg, 1.78 mmol),  
5 K<sub>2</sub>CO<sub>3</sub> (517 mg, 3.74 mmol), CHCl<sub>3</sub> (4 mL), H<sub>2</sub>O (2 mL) and cyclopentyl chloroformate (511 mg, 3.74 mmol). After basic treatment for 1 h the mixture was acidified to pH 9 with aq. 1M HCl. The reaction mixture was extracted with CHCl<sub>3</sub> (3x) and the combined org. phases were dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure and the residue purified by RP-HPLC (95% H<sub>2</sub>O → 65% H<sub>2</sub>O over 10  
10 min → 0% H<sub>2</sub>O over 10 min). Cyclopentyl 4-ethyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate was obtained as foam (174 mg, 26%). t<sub>R</sub> = 10.14 min. <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD): δ = 8.75 (s); 5.17 (s, br., 1H); 5.12 (t, J = 5.4 Hz, 1H); 3.21 (s, br., 1H); 2.76 (m, 1H); 2.68 (dd, J<sub>1</sub> = 14.9 Hz, J<sub>2</sub> = 3.4 Hz, 1H); 1.95-1.58 (m, 10H); 1.02 (t, J = 7.3 Hz, 3H). <sup>13</sup>C-NMR (100 MHz, CD<sub>3</sub>OD): δ  
15 = 157.00 (s); 134.08 (d); 129.71 (s); 127.70 (s); 80.44 (d); 52.48 (d); 37.72 (t); 33.78 (t); 27.86 (t); 24.61 (t); 22.00 (t); 10.95 (q). MS (EI): m/z = 263 (M<sup>+</sup>, 4%); 234 (48%); 194 (12%); 178 (12%); 166 (100%); 122 (33%); 120 (14%); 107 (5%); 93 (5%). HRMS: Calc. for C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>: M<sup>+</sup> = 263.1634; found: 263.1595.

Example 18:

Cyclopentyl 4-propyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate: According to *GP/II*, starting from 4-propyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride (400 mg, 1.68 mmol),  
20 K<sub>2</sub>CO<sub>3</sub> (487 mg, 3.53 mmol), CHCl<sub>3</sub> (4 mL), H<sub>2</sub>O (2 mL) and cyclopentyl chloroformate (482 mg, 3.53 mmol). After basic treatment for 1 h the mixture was acidified to pH 8-9 with aq. 1M HCl. The reaction mixture was extracted with CHCl<sub>3</sub>  
25 (4x) and the combined org. phases were dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure and the residue purified by RP-HPLC (95% H<sub>2</sub>O → 65% H<sub>2</sub>O over 10 min → 0% H<sub>2</sub>O over 10 min). Cyclopentyl 4-propyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate was obtained as foam (106  
30 mg, 27%). t<sub>R</sub> = 10.97 min. <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD): δ = 8.75 (s, 1H); 5.25 (m, br., 1H); 5.11 (s, br., 1H); 4.38 (m, br., 1H); 3.22 (m, br., 1H); 2.77 (m, br., 1H); 2.68 (dd, J<sub>1</sub> = 15.9 Hz, J<sub>2</sub> = 4.4 Hz, 1H); 1.95-1.58 (m, 10H); 1.46 (m, 12H); 1.00 (t, J = 7.3 Hz,

- 3H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  = 134.05 (d); 129.87 (s); 127.67 (s); 80.47 (d); 51.03 (d); 38.10 (t); 36.99 (t); 33.79 (t); 24.59 (t); 21.91 (t); 20.34 (t); 14.12 (q). MS (EI):  $m/z$  = 277 ( $\text{M}^+$ , 1%); 234 (32%); 208 (9%); 192 (10%); 166 (74%); 164 (7%); 150 (4%); 135 (5%); 122 (36%); 120 (49%); 95 (15%); 69 (100%). HRMS: Calc. for  $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_2$ :  $\text{M}^+$  = 277.1790; found: 277.1780.

Example 19:

- Cyclopentyl 4-phenyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate:** According to *GPII*, starting from 4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride (500 mg, 1.59 mmol),  $\text{K}_2\text{CO}_3$  (461 mg, 3.34 mmol),  $\text{CHCl}_3$  (5 mL),  $\text{H}_2\text{O}$  (2.5 mL) and cyclopentyl chloroformate (456 mg, 3.34 mmol). After basic treatment for 1 h the mixture was acidified to pH 8-9 with aq. 1M HCl. The reaction mixture was extracted with  $\text{CHCl}_3$  (4x) and the combined org. phases were dried over  $\text{Na}_2\text{SO}_4$ . The solvent was removed under reduced pressure and the residue purified by RP-HPLC (95%  $\text{H}_2\text{O}$   $\rightarrow$  65%  $\text{H}_2\text{O}$  over 10 min  $\rightarrow$  0%  $\text{H}_2\text{O}$  over 10 min). Cyclopentyl 4-phenyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate was obtained as foam (162 mg, 24%) that contained 1 eq.  $\text{H}_2\text{O}$  according to the elemental analysis.  $t_R$  = 10.35 min.  $^1\text{H}$ -NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  = 8.83 (s, 1H); 7.43-7.35 (m, 3H); 7.32-7.27 (m, 2H); 6.44 (s, br., 1H); 5.16 (s, br., 1H); 4.34 (s, br., 1H); 3.18 (m, 1H); 2.91 (dd,  $J_1$  = 16.1 Hz,  $J_2$  = 5.9 Hz, 1H); 2.83 (dd,  $J_1$  = 16.4 Hz,  $J_2$  = 4.9 Hz, 1H); 1.97-1.56 (m, 8H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  = 139.24 (s); 134.90 (d); 129.90 (d); 129.84 (d); 129.43 (s); 128.89 (d); 127.38 (s); 80.75 (d); 54.01 (d); 38.01 (t); 33.84 (t); 33.71 (t); 24.58 (t); 22.18 (t). MS (EI):  $m/z$  = 311 ( $\text{M}^+$ , 56%); 242 (100%); 226 (24%); 198 (91%); 169 (72%); 166 (39%); 122 (13%). HRMS: Calc. for  $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_2$ :  $\text{M}^+$  = 311.1634; found: 311.1625. Elemental analysis: Calc. for  $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_2 \cdot \text{C}_2\text{HF}_3\text{O}_2 \cdot \text{H}_2\text{O}$ : C 54.2%, H 5.5%, N 9.5%; found: C 54.1%, H 5.4%, N 9.4%.

Example 20:

- 4-Fluorophenyl 4-ethyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate:** According to *GPII*, starting from 4-ethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride (400 mg, 1.78 mmol),  $\text{K}_2\text{CO}_3$  (517 mg, 3.74 mmol),  $\text{CHCl}_3$  (4 mL),  $\text{H}_2\text{O}$  (2 mL) and 4-fluorophenyl chloroformate (0.49 mL, 3.7 mmol). After basic treatment for 1 h the mixture was acidified to pH 9 with aq. 1M HCl. The reaction mixture was extracted with  $\text{CHCl}_3$  (3x) and the

combined org. phases were dried over  $\text{Na}_2\text{SO}_4$ . The solvent was removed under reduced pressure, the residue taken in aq. 1M HCl and washed with  $\text{Et}_2\text{O}$  (1x). The aq. phase was evaporated under reduced pressure and the residue was purified by RP-HPLC (90%  $\text{H}_2\text{O}$   $\rightarrow$  65%  $\text{H}_2\text{O}$  over 10 min  $\rightarrow$  5%  $\text{H}_2\text{O}$  over 10 min). **4-Fluorophenyl 4-ethyl-**

- 5 **1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate** was obtained as foam (64 mg, 9%).  $t_R = 9.21$  min.  $^1\text{H-NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta = 8.80$  (s, 1H); 7.12 (m, 4H); 5.81 (m, br., 1H); 4.55 (m, br., 1H); 3.44 (m, br., 1H); 2.97 (m, br., 1H); 2.81 (m, br., 1H); 1.96 (m, br., 2H); 1.12 (m, br., 3H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta = 161.44$  (sd,  $J_F = 182$  Hz); 155.77 (s); 148.38 (s); 134.25 (d); 129.36 (s);  
10 127.63 (s); 124.33 (d); 116.76 (sd,  $J_F = 17$  Hz); 53.01 (d); 38.31 (t); 27.62 (t); 22.39 (t); 10.84 (q). MS (EI):  $m/z = 289$  ( $M^+$ , 6%); 260 (100%); 178 (77%); 122 (12%); 120 (12%); 112 (7%); 95 (15%). HRMS: Calc. for  $\text{C}_{15}\text{H}_{16}\text{FN}_3\text{O}_2$ :  $M^+ = 289.1227$ ; found: 289.1228.

Example 21:

- 15 **4-Fluorophenyl 4-propyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate**: According to *GPII*, starting from 4-propyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride (400 mg, 1.68 mmol),  $\text{K}_2\text{CO}_3$  (487 mg, 3.53 mmol),  $\text{CHCl}_3$  (4 mL),  $\text{H}_2\text{O}$  (2 mL) and 4-fluorophenyl chloroformate (0.47 mg, 3.6 mmol). After basic treatment for 1 h the mixture was acidified to pH 8-9  
20 with aq. 1M HCl. The reaction mixture was extracted with  $\text{CHCl}_3$  (4x) and the combined org. phases were dried over  $\text{Na}_2\text{SO}_4$ . The solvent was removed under reduced pressure and the residue purified by FC ( $\text{MeOH}/\text{CHCl}_3$  2:98  $\rightarrow$  5:95  $\rightarrow$  10:90  $\rightarrow$  1:1). **4-Fluorophenyl 4-propyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate trifluoroacetate** was obtained as foam (92 mg, 18%).  $R_f = 0.20$   
25 ( $\text{MeOH}/\text{CHCl}_3$  1:9).  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.80$  (s, br., 1H); 7.03 (m, br., 4H); 7.23 and 4.93 (m, 1H, rot.); 4.45 and 4.36 (m, 1H, rot.); 3.43-3.09 (m, 1H); 2.88-2.76, 2.69-2.46 and 2.32-2.18 (m, 2H, rot.); 1.93-1.33 (m, 2H, rot.); 0.98-0.87 (m, 3H, rot.).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 159.93$  (sd,  $J_F = 182$  Hz); 154.43 (s); 147.15 (s); 134.15 (d); 123.09 (d); 115.88 (dd,  $J_F = 18$  Hz); 53.16 and 52.58 (d, rot.); 38.96 and  
30 38.74 (t, rot.); 37.01 and 36.64 (t, rot.); 23.36 and 22.27 (t, rot.); 19.67 and 19.34 (t, rot.); 14.34 and 14.18 (q, rot.). MS (EI):  $m/z = 303$  ( $M^+$ , 2%); 260 (100%); 224 (5%); 208 (7%); 150 (19%); 122 (17%); 112 (10%). HRMS: Calc. for  $\text{C}_{16}\text{H}_{18}\text{FN}_3\text{O}_2$ :  $M^+ = 303.1383$ ; found: 303.1392.

Example 22:

**Methoxy-ethyl 4-ethyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate:** According to *GP11*, starting from 4-ethyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride (400 mg, 1.78 mmol), K<sub>2</sub>CO<sub>3</sub> (517 mg, 3.74 mmol), CHCl<sub>3</sub> (4 mL), H<sub>2</sub>O (2 mL) and methoxyethyl chloroformate (518 mg, 3.74 mmol). After basic treatment for 1 h the mixture was acidified to pH 9 with aq. 1M HCl. The reaction mixture was extracted with CHCl<sub>3</sub> (3x) and the combined org. phases were dried over Na<sub>2</sub>SO<sub>4</sub>. The residue was purified by FC (MeOH/CHCl<sub>3</sub> 2:98 → 5:95 → 10:90). **Methoxy-ethyl 4-ethyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate** was obtained as foam (98 mg, 22%) that contained 0.5 eq. H<sub>2</sub>O according to the elemental analysis. R<sub>f</sub> = 0.05 (MeOH/CHCl<sub>3</sub> 1:9). <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD): δ = 7.55 (s, 1H); 5.00 (s, br., 1H); 4.35 (m, br., 1H); 4.24 (s, br., 2H); 3.60 (s, br., 2H); 3.35 (s, br., 3H); 3.18 (s, br., 1H); 2.71 (ddd, J<sub>1</sub> = 16.4 Hz, J<sub>2</sub> = 12.0 Hz, J<sub>3</sub> = 5.6 Hz, 1H); 2.53 (dd, J<sub>1</sub> = 15.4 Hz, J<sub>2</sub> = 3.4 Hz, 1H); 1.89 (m, 1H); 1.71 (m, 1H); 1.00 (t, J = 7.3 Hz, 3H). <sup>13</sup>C-NMR (100 MHz, CD<sub>3</sub>OD): δ = 157.50 (s); 135.22 (d); 133.67 (s); 126.64 (s); 71.86 (t); 65.80 (t); 59.06 (q); 54.81 (d); 39.18 and 38.88 (t, rot.); 28.49 and 28.27 (t, rot.); 23.59 and 23.07 (t, rot.); 11.14 (q). MS (EI): m/z = 253 (M<sup>+</sup>, 6%); 224 (100%); 194 (4%); 166 (7%); 150 (3%); 122 (38%). HRMS: Calc. for C<sub>12</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>: M<sup>+</sup> = 253.1426; found: 253.1421. Elemental analysis: Calc. for C<sub>12</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub>·1/2H<sub>2</sub>O: C 54.95%, H 7.68%, N 16.07%; found: C 55.07%, H 7.81%, N 15.78%.

Example 23:

**Methoxyethyl 4-propyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate:** According to *GP11*, starting from 4-propyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride (400 mg, 1.68 mmol), K<sub>2</sub>CO<sub>3</sub> (487 mg, 3.53 mmol), CHCl<sub>3</sub> (4 mL), H<sub>2</sub>O (2 mL) and methoxyethyl chloroformate (490 mg, 3.53 mmol). After basic treatment for 1 h the mixture was acidified to pH 8-9 with aq. 1M HCl. The reaction mixture was extracted with CHCl<sub>3</sub> (4x) and the combined org. phases were dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure and the residue purified by FC (MeOH/CHCl<sub>3</sub> 2:98 → 5:95 → 10:90). **Methoxyethyl 4-propyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate** was obtained as foam (87 mg, 20%) that contained 0.25 eq. H<sub>2</sub>O according to the elemental analysis. R<sub>f</sub> = 0.25 (MeOH/CHCl<sub>3</sub> 1:9). <sup>1</sup>H-NMR (400 MHz, CD<sub>3</sub>OD): δ = 7.51 (s, 1H); 5.08 (s, br., 1H); 4.32 (m, br., 1H); 4.23 (m, br., 2H); 3.59 (s, br., 2H); 3.36 and 3.34 (s, 3H, rot.); 3.17

(m, br., 1H); 2.70 (ddd,  $J_1 = 16.1$  Hz,  $J_2 = 12.0$  Hz,  $J_3 = 5.6$  Hz, 1H); 2.53 (dd,  $J_1 = 15.4$  Hz,  $J_2 = 3.2$  Hz, 1H); 1.79 (m, 1H); 1.70 (m, 1H); 1.45 (m, 2H); 0.97 (t,  $J = 7.6$  Hz, 3H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta = 157.44$  (s); 135.22 (d); 133.93 (s); 126.82 (s); 71.84 (t); 65.79 (t); 59.05 (q); 53.30 (d); 39.10 and 38.80 (t, rot.); 37.71 and 37.46 (t, rot.); 23.59 and 23.06 (t, rot.); 20.49 (t); 14.41 (q). MS (EI):  $m/z = 267$  ( $\text{M}^+$ , 7%); 224 (100%); 208 (6%); 192 (7%); 180 (12%); 166 (11%); 122 (62%). HRMS: Calc. for  $\text{C}_{13}\text{H}_{21}\text{N}_3\text{O}_3$ :  $\text{M}^+ = 267.1581$ ; found: 267.1582. Elemental analysis: Calc. for  $\text{C}_{13}\text{H}_{21}\text{N}_3\text{O}_3 \cdot 1/4\text{H}_2\text{O}$ : C 57.44%, H 7.97%, N 15.52%; found: C 57.28%, H 8.11%, N 15.22%.

10 **Example 24:**

**Methoxyethyl 4-phenyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate:** According to *GP II*, starting from 4-phenyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride (500 mg, 1.59 mmol),  $\text{K}_2\text{CO}_3$  (461 mg, 3.34 mmol),  $\text{CHCl}_3$  (6 mL),  $\text{H}_2\text{O}$  (4 mL) and methoxyethyl chloroformate (462 mg, 3.34 mmol). After basic treatment for 1 h the mixture was acidified to pH 8-9 with aq. 1M HCl. The reaction mixture was extracted with  $\text{CHCl}_3$  (4x) and the combined org. phases were dried over  $\text{Na}_2\text{SO}_4$ . The solvent was removed under reduced pressure and the residue purified by FC ( $\text{MeOH}/\text{CHCl}_3$  2:98  $\rightarrow$  5:95  $\rightarrow$  10:90). **Methoxyethyl 4-phenyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate** was obtained as foam (267 mg, 56%).  $R_f = 0.26$  ( $\text{MeOH}/\text{CHCl}_3$  1:9).  $^1\text{H}$ -NMR (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta = 7.62$  (s, 1H); 7.30 (m, 5H); 6.30 (s, br., 1H); 4.29 (m, br., 2H); 3.65 (m, br., 2H); 3.38 (s, 3H); 3.09 (m, 1H); 2.82 (m, br., 1H); 2.65 (m, br., 1H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta = 157.09$  (s); 141.43 (s); 135.89 (d); 131.30 (s); 129.25 (d); 129.03 (d); 128.77 (d); 128.34 (s); 77.81 (t); 65.99 (t); 59.08 (q); 56.09 (d); 38.95 and 38.81 (t, rot.); 23.51 and 23.07 (t, rot.). MS (EI):  $m/z = 301$  ( $\text{M}^+$ , 24%); 242 (26%); 198 (41%); 115 (10%); 88 (11%). HRMS: Calc. for  $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}_3$ :  $\text{M}^+ = 301.1426$ ; found: 301.1419.

25 **Example 25:**

**Benzyl 4-methyl-1,4,6,7-tetrahydro-5H-imidazo[4,5-c]pyridine-5-carboxylate:** According to *GP II*, starting from 4-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine dihydrochloride (500 mg, 2.38 mmol),  $\text{K}_2\text{CO}_3$  (690 mg, 5.00 mmol),  $\text{CHCl}_3$  (6 mL),  $\text{H}_2\text{O}$  (3 mL) and benzyl chloroformate (0.75 mL, 5.0 mmol). The reaction was carried out in a parallel fashion in a test-tube closed with a screwed tap and stirred in a *Stem*-stirrer. The basic treatment was carried out in MeOH (6 mL)